



Hyper-IgD and periodic fever syndrome: a new *MVK* mutation (p.R277G) associated with a severe phenotype



Joana A. Santos^{a,*}, Juan I. Aróstegui^b, Maria J. Brito^c, Conceição Neves^d, Marta Conde^e

^a Pediatric Department, Hospital Dona Estefânia, CHLC, EPE, Lisbon, Portugal

^b Immunology Department, Hospital Clínic-IDIBAPS, Barcelona, Spain

^c Pediatric Infectious Diseases Unit, Hospital Dona Estefânia, CHLC, EPE, Lisbon, Portugal

^d Primary Immunodeficiency, Hospital Dona Estefânia, CHLC, EPE, Lisbon, Portugal

^e Pediatric Rheumatology, Hospital Dona Estefânia, CHLC, EPE, Lisbon, Portugal

ARTICLE INFO

Article history:

Received 25 August 2013

Received in revised form 18 February 2014

Accepted 15 March 2014

Available online 18 March 2014

Keywords:

Hyperimmunoglobulinemia D and periodic fever syndrome
Mevalonate kinase
New mutation
Phenotype
Anakinra

ABSTRACT

Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS; MIM# 260920) is a rare recessively-inherited autoinflammatory condition caused by mutations in the *MVK* gene, which encodes for mevalonate kinase, an essential enzyme in the isoprenoid pathway. HIDS is clinically characterized by recurrent episodes of fever and inflammation. Here we report on the case of a 2 year-old Portuguese boy with recurrent episodes of fever, malaise, massive cervical lymphadenopathy and hepatosplenomegaly since the age of 12 months. Rash, arthralgia, abdominal pain and diarrhea were also seen occasionally. During attacks a vigorous acute-phase response was detected, including elevated erythrocyte sedimentation rate, C-reactive protein, serum amyloid A and leukocytosis. Clinical and laboratory improvement was seen between attacks. Despite normal serum IgD level, HIDS was clinically suspected. Mutational *MVK* analysis revealed the homozygous genotype with the novel p.Arg277Gly (p.R277G) mutation, while the healthy non-consanguineous parents were heterozygous. Short nonsteroidal anti-inflammatory drugs and corticosteroid courses were given during attacks with poor benefits, whereas anakinra showed positive responses only at high doses. The p.R277G mutation here described is a novel missense *MVK* mutation, and it has been detected in this case with a severe HIDS phenotype. Further studies are needed to evaluate a co-relation genotype, enzyme activity and phenotype, and to define the best therapeutic strategies.

© 2014 Elsevier B.V. All rights reserved.

1. Introduction

Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS; MIM# 260920) is a rare autosomal recessive autoinflammatory condition caused by mutations in the *MVK* gene, which encodes for mevalonate kinase, an essential enzyme in the isoprenoid and cholesterol biosynthesis

pathway (Bader-Meunier et al., 2011; Korppi et al., 2011; van der Hilst and Frenkel, 2010). The disease is clinically characterized by recurrent episodes of fever and inflammation. Starting in the first year of life, patients have periodic fever episodes lasting four to six days, at variable intervals, with accompanying lymphadenopathy, hepatosplenomegaly, gastrointestinal complaints, aphthous ulcers, arthralgias, and skin rashes (Bader-Meunier et al., 2011; Korppi et al., 2011; Lierl, 2007; van der Burgh et al., 2012; van der Hilst and Frenkel, 2010). Some episodes are triggered by immunizations, stress, infection, or minor trauma (Korppi et al., 2011; van der Hilst and Frenkel, 2010). AA-type amyloidosis has been very rarely reported in HIDS patients, with less than 10 cases currently described, an incidence considerably lower than that found in other inherited autoinflammatory syndromes (van der Hilst and Frenkel, 2010). Laboratory evaluation at the time of attack reveals a vigorous acute phase response, with elevated erythrocyte sedimentation rate (ESR), granulocytosis, raised serum concentrations of C-reactive protein (CRP) and serum amyloid A (SAA). Polyclonal serum IgD elevation has been considered the hallmark of the disease. However, the serum IgD elevation is not obligatory and IgD values may be normal, especially in young children. Serum IgA levels are also often elevated in most patients with HIDS. During attacks, mevalonic acid urinary excretion is slightly elevated, and its measurement can be of diagnostic value (Bader-Meunier

Abbreviations: ANA, antinuclear antibodies; ANCAs, antineutrophil cytoplasmic antibodies; Arg (or R), arginine; C, cysteine; CD, cluster of differentiation; cm, centimeter(s); CMV, cytomegalovirus; CRP, C-reactive protein; dL, deciliter(s); DNA, deoxyribonucleic acid; ds, double strand(ed); EBV, Epstein–Barr virus; ENAs, extractable nuclear antigens; ESR, erythrocyte sedimentation rate; g, gram(s); Gly (or G), glycine; h, hour; H, histidine; HbA2, hemoglobin A2; HHV, human herpes virus; HIDS, Hyperimmunoglobulinemia D and periodic fever syndrome; HIV, human immunodeficiency virus; I, isoleucine; Ig, immunoglobulin; IL, interleukin; kg, kilogram(s); L, liter(s); MA, mevalonic aciduria; mg, milligram(s); MIM, Mendelian Inheritance in Man; mm, millimeter(s); mm³, cubic millimeter(s); *MVK*, mevalonate kinase; n, number; NSAID, nonsteroidal anti-inflammatory drug; p, amino acid substitution; q, long arm; SAA, serum amyloid A; sc, subcutaneous; SIFT, Sorting Intolerant From Tolerant; sp., species; T, threonine; TNF, tumor necrosis factor; V, valine; WBC, white blood cell(s); wt, wild type.

* Corresponding author at: Hospital Dona Estefânia, Centro Hospitalar Lisboa Central, EPE, Rua Jacinta Marto, 1169-045 Lisbon, Portugal.

E-mail addresses: joanaasantos@gmail.com (J.A. Santos), JIAROSTE@clinic.ub.es (J.I. Aróstegui), joao.rochabrito@netcabo.pt (M.J. Brito), conceicaoaneves59@gmail.com (C. Neves), marta.c.conde@gmail.com (M. Conde).

et al., 2011; Korppi et al., 2011; van der Hilst and Frenkel, 2010). On the other hand, cellular and humoral immunity tests, as well as serum complement levels, are normal in HIDS patients, with undetected autoantibodies (Lierl, 2007). Currently, there is no evidence-based treatment available for HIDS (Korppi et al., 2011). Thus far, some children have been successfully treated with etanercept and others with IL-1 antagonists (Bodar et al., 2011; Caorsi et al., 2012; Galeotti et al., 2012; Hoffman, 2009; Rigante et al., 2006).

2. Clinical report

A 2 year-old Portuguese boy, with age-appropriate weight (75th percentile) and height (75th percentile), and normal cognitive development, presented with recurrent episodes of fever (3–5-day duration, every 2–5 weeks) and malaise, massive cervical lymphadenopathy and hepatosplenomegaly (6–7 cm), since the age of 17, 18, and 21 months. Skin rash, arthralgia, abdominal pain and diarrhea were seen occasionally on crises. Laboratory evaluation revealed mild microcytic hypochromic anemia (hemoglobin 8–10 g/dL), with a Mentzer index suggestive of iron-deficiency anemia (greater than 13), with no response to iron supplementation and, during acute attacks, leukocytosis (white blood cell count 23,490–32,280/mm³) with neutrophilia (67.8–80.9%), increased ESR (61–91 mm/h; normal range: less than 15 mm/h) and CRP (6.27–18.49 mg/dL; normal range: less than 0.5 mg/dL). Clinical and laboratory improvement, though incomplete, was seen in-between (Table 1).

The patient was extensively studied. Renal and liver functions, as well as cardiac, ophthalmologic and neurologic evaluations were normal. Infectious causes, namely virus (HIV 1–2, EBV, CMV, HHV 6–7), parasites (*Toxoplasma gondii*, *Leishmania* sp.), and bacteria (*Mycobacterium tuberculosis*, atypical mycobacteria, *Bartonella henselae*, *Brucella* sp., *Rickettsia* sp., *Coxiella burnetii*, *Ehrlichia*) were ruled out. Child immune status was normal, ruling out primary immunodeficiency disorders like autoimmune lymphoproliferative syndrome, chronic granulomatous disease and leukocyte adhesion deficiency. Bone marrow and lymph node examination also excluded lymphoproliferative disease. Autoimmune evaluation was negative (ANA, ENAs, anti-dsDNA, ANCAs and complement) excluding autoimmune disease.

SAA increased to 104–510 mg/L (reference range: <6.4 mg/L), and serum IgA was 2.5–4.9 g/L (normal range: 0.45–1.35 g/L) (Table 1). Despite normal serum IgD (less than 22.6 mg/L), HIDS was clinically suspected. Mutational MVK analysis revealed a homozygous genotype for a new missense variant p.Arg277Gly (p.R277G) in the patient, and heterozygous genotypes for the healthy non-consanguineous parents (Fig. 1). In silico analyses using the SIFT and Polyphen-2 algorithms reveal respectively a tolerated (Score 0.28) and possibly damaging (Score 0.952) behavior for the structure and/or function of mevalonate kinase protein.

At the time of diagnosis, short corticosteroid (2 mg/kg/day for 3 days, with tapering in 5 days) and nonsteroidal anti-inflammatory drug (NSAID) courses were given during attacks, with poor benefits

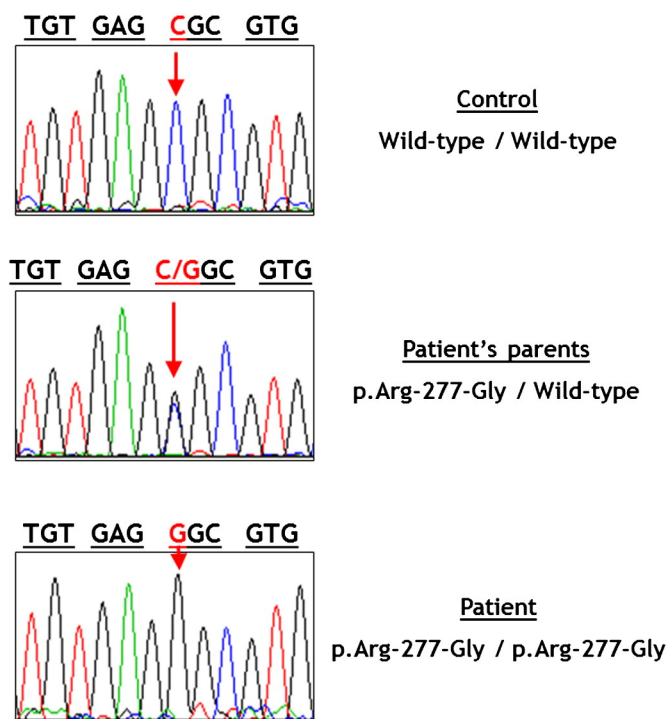


Fig. 1. Chromatograms showing the patient's homozygous p.Arg277Gly/p.Arg277Gly MVK genotype (bottom panel), the heterozygous p.Arg277Gly/wt MVK genotype of patient's parents (middle panel) and a healthy control (upper panel).

mainly characterized for the decrease of fever duration. On the basis of frequent crises and subclinical inflammation between episodes (elevated CRP, ESR and SAA) (Table 1), subcutaneous (sc) anakinra was started (2 mg/kg/day) at the age of 3 years. He showed initially a good response to this treatment, characterized by decrease of frequency of episodes (only two crises in 5 months) and reduced severity of crisis (one day of mild fever without malaise; skin rash for 5–7 days, no lymphadenopathy and hepatosplenomegaly, nor vomiting or diarrhea). After these five months of anakinra therapy he restarted with severe crises and dose was increased to 3 mg/kg/day sc. Crises were characterized by ill appearing, high fevers, skin rash, cervical adenopathy, hepatomegaly (4 cm), splenomegaly (4 cm), abdominal pain, diarrhea, and serositis in 2 episodes. During these acute attacks he also had leukocytosis, increased ESR and CRP, and, for the first time, a serum IgD rise (Table 1). Frequently, steroid courses should be added to anakinra to control these crises. Six months later, anakinra dose was increased to 5 mg/kg/day because of monthly crises and persistent inflammatory markers out of crises. With this scheme severe crises became less frequent, anemia improved with normalization of red blood cell indices and normal HbA₂ level, and, at the same time, there was a normalization of inflammatory markers detected, with normal SAA and CRP; ESR 16 mm/h. Serum IgD levels keep high (458 mg/L), with IgA also above

Table 1
Clinical and laboratory data before and upon the treatment with anakinra.

Laboratory evaluation	Before anakinra		Upon anakinra 2–3 mg/kg/day	Upon anakinra 5 mg/kg/day
	On crisis	Between crises		
Hemoglobin (g/dL)	8	8.6	10.3–10.6	10.7
WBC count/mm ³	32,280	19,390	15,200–18,400	9800
Platelets/mm ³	849,000	422,000	239,000–408,000	421,000
ESR (mm/h)	120	91	53–104	16
CRP (mg/dL)	26.81	15.87	8.19–14.8	0.59
SAA (mg/L)	510	–	93.4	12.7
IgA (g/L)	4.9	3.71	2.12–2.66	3.49
IgD (mg/L)	<22.6	<22.6	92.7–151.2	458
Crises	Every 2–5 weeks	–	7 crises in 11 months; 3 times corticosteroid	4 crises in 34 months; 2 times corticosteroid

normal values (Table 1). The peripheral blood B cell immunophenotyping performed under anakinra therapy revealed the presence of very few class-switch CD19 + CD27 + IgD-cells, with excess of B cells exhibiting the naïve phenotype. Three years later, on anakinra 5 mg/kg/day, the patient is stable, with few crises and normal or almost normal inflammatory markers most of the time.

3. Discussion

MVK gene is located on chromosome 12q24, and around 65 different mutations have been currently identified. Most of them are loss-of-function mutations and are associated with a wide phenotypic spectrum, probably related with the residual activity of the patient's mevalonate kinase enzyme. The extremes of this spectrum are the HIDS syndrome at the less severe end and the mevalonic aciduria (MA) at the severest. In HIDS, the residual enzymatic activity varies from 1% to 10% and it is less than 0.5% in MA (Bader-Meunier et al., 2011; Korppi et al., 2011; van der Hilst and Frenkel, 2010). However, within the HIDS phenotype there is no clear relationship among severity of disease, symptoms onset, number of attacks per year, and a specific mutation (van der Hilst and Frenkel, 2010). Interestingly, some families with HIDS carry at least one of the MVK mutations responsible for MA, such as p.I268T. On the other hand, the incidence of the most commonly HIDS-associated mutation (p.V377I) in Dutch population is significantly higher than would be anticipated based on the number of diagnosed cases of HIDS in Holland (about 2:100,000 live births) (Lierl, 2007). This implies that some individuals who are homozygous for this mutation do not develop HIDS. The reason for the differing phenotypes produced by this genetic variant has not been still determined (Lierl, 2007). In this patient, mutational MVK analysis revealed a homozygous genotype for a new missense variant p.Arg277Gly (p.R277G), while the healthy non-consanguineous parents were heterozygous. The p.R277G MVK variant has not been previously reported in the medical literature and registered neither in the INFEVERS database nor in the online available database dbSNP, supporting reasonably its exclusion as a rare gene polymorphism. The p.R277G variant has not been registered in different database of genomic Diversity (1000 Genome Project, HapMap, etc.). In this database are included samples from different ancestries and origins, including samples from the Iberian Peninsula. In the authors' personal experience, this particular MVK variant has not been detected in approximately 1400 MVK alleles analyzed during the past decade, from both Spanish patients (n approx: 600) and controls (n: 100). Interestingly, in the INFEVERS database two different MVK mutations affecting the same amino acid residue have been registered: i) the p.R277C MVK mutation detected in a patient with mevalonic aciduria (Houten et al., 2000) and ii) the p.R277H MVK mutation detected in a family with HIDS (Hospach et al., 2005). These evidences strongly suggest that the amino acid residue arginine at position 277 could be an important residue for the enzymatic activity of the protein mevalonate kinase. The activity of the mevalonate kinase, not performed, would be relevant in helping to demonstrate the importance of this mutation and a possible explanation for the severity of this patient's disease. Additionally, the bioinformatics analyses of the novel MVK variant, using the SIFT and Polyphen-2 algorithms, predict a tolerated and possibly damaging behavior, respectively.

Mevalonate kinase is an essential enzyme for isoprenoid metabolism, which produces cholesterol, ubiquinone and dolichol, which play a role in protein isoprenylation (van der Hilst and Frenkel, 2010). How mevalonate kinase deficiency leads to inflammation is incompletely understood, with two major hypotheses for the disease's pathogenesis: the accumulation of products upstream of the step catalyzed by the mevalonate kinase enzyme, such as mevalonic acid, or the marked reduction of products downstream this step, including cholesterol or isoprenoids (Stojanov and Kastner, 2005). These latter compounds are involved in the post-translational isoprenylation (farnesylation or geranylation) of several important intracellular signaling molecules,

including the Ras, Rho/Rac, and Rab families of small guanosine triphosphate-binding proteins. In an in vitro system, accentuated IL-1 β secretion by leukocytes from HIDS patients can be reversed by the addition of farnesol or geranyl-geraniol, leading support to the second hypothesis (Stojanov and Kastner, 2005). Both the isoprenoid deficiency and the mevalonate accumulation hypotheses predict symptoms worsening with decreased mevalonate kinase enzymatic activity (Stojanov and Kastner, 2005). Accordingly, the level of mevalonic acid excreted in urine is admitted to be of diagnostic value.

HIDS clinical picture is believed to reflect enhanced proinflammatory cytokine production by mononuclear cells (Lachmann et al., 2011; Touitou and Koné-Paut, 2008). A defect in lymphocyte apoptosis has also been detected (van der Hilst and Frenkel, 2010). The proinflammatory state, with subsequent tumor necrosis factor alpha (TNF- α) and interleukin 1-beta (IL-1 β) overproduction, is believed to induce the disease's characteristic attacks and inflammatory markers (Lachmann et al., 2011; Touitou and Koné-Paut, 2008). Even between attacks, about half the patients have signs of inflammation with SAA and CRP elevation, although much lower than during attacks (van der Hilst and Frenkel, 2010), as reported in this patient.

The principal laboratory finding in HIDS is a persistent elevation of polyclonal IgD. However, IgD values can be within normal range, especially until 3 years of age (van der Hilst and Frenkel, 2010). In fact, it has been reported that symptoms may precede the increase in serum IgD concentrations by years, and the levels of IgD do not correlate with the frequency or severity of attacks (Saulsbury, 2003). Increased serum IgA levels have been found in >80% of patients with HIDS (Klasen et al., 2001). Likewise, this patient had normal serum IgD (until 3 years old) and elevated IgA levels since disease's onset. Klasen IS et al. provided evidence that elevated IgA levels in HIDS is due to a systemic stimulation of the immune system with a continuous stimulation of the IgA system (Klasen et al., 2001). Interestingly, hyper-IgA in HIDS is mostly represented by hyper-IgA1, suggesting bone marrow as the main production site of IgA. The significant correlation between IgA or IgA1 and IgD suggests a collective stimulatory site (Klasen et al., 2001). In this patient, the peripheral blood B cell immunophenotyping revealed the presence of very few class-switch CD19 + CD27 + IgD-cells, with excess of B cells exhibiting the naïve phenotype. These cells may be responsible for the IgD production. We believe that the virtual absence of IgA1 producing plasmocytes may be explained by their preferential location in the bone marrow.

Currently, there is no evidence-based treatment available for HIDS and targeted therapies are needed (van der Burgh et al., 2012). Etanercept, a TNF- α inhibitor, and anakinra, the recombinant form of the human IL-1 receptor antagonist, are reasonable alternatives in the treatment of HIDS, as these cytokines seem to play a central role in acute HIDS attacks. Infliximab, a humanized monoclonal antibody against TNF- α , and tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, might also be thinkable alternatives. So far, some children have been successfully treated with etanercept and with different anti-IL-1 drugs (Bodar et al., 2011; Caorsi et al., 2012; Galeotti et al., 2012; Hoffman, 2009; Rigante et al., 2006). If either of these treatments are not effective a switch to the other can be considered, because some patients have a good response to anti-IL1 drugs but not to etanercept, and vice versa (Caorsi et al., 2012; van der Hilst and Frenkel, 2010). Severe unresponsive cases of MA could be considered for allogeneic stem cell transplantation (van der Burgh et al., 2012). In the case here described only a partial clinical response to usual doses of anakinra (2 mg/kg/day) was initially observed, requiring step-up doses reaching 5 mg/kg/day to achieve a more controlled disease (inflammatory markers, less number of crises and severe ones with need for steroid therapy). These findings, along with severity of the clinical picture and persistently elevated inflammatory parameters, including SAA, are consistent with the presence of a severe phenotype.

Advances in our understanding of HIDS pathogenesis may allow explaining the differences in treatment response and its possible

relation to the different genotypes. Further studies are needed to evaluate a relation MVK genotype, enzyme activity and clinical phenotype, and to define best therapeutic strategies for each patient.

Conflict of interest

There is no conflict of interest.

References

- Bader-Meunier, B., Florkin, B., Sibilia, J., Acquaviva, C., Hachulla, E., Grateau, G., Richer, O., Farber, C.M., Fischbach, M., Hentgen, V., Jegou, P., Laroche, C., et al., 2011. Mevalonate kinase deficiency: a survey of 50 patients. *Pediatrics* 128 (1), 152–159.
- Bodar, E.J., Kuijk, L.M., Drenth, J.P., van der Meer, J.W., Simon, A., Frenkel, J., 2011. On-demand anakinra treatment is effective in mevalonate kinase deficiency. *Annals of the Rheumatic Diseases* 70 (12), 2155–2158.
- Caorsi, R., Federici, S., Gattorno, M., 2012. Biologic drugs in autoinflammatory syndromes. *Autoimmunity Reviews* 12 (1), 81–86.
- Galeotti, C., Meinzer, U., Quartier, P., Rossi-Semerano, L., Bader-Meunier, B., Pillet, P., Koné-Paut, I., 2012. Efficacy of interleukin-1-targeting drugs in mevalonate kinase deficiency. *Rheumatology (Oxford)* 51 (10), 1855–1859.
- Hoffman, H.M., 2009. Therapy of autoinflammatory syndromes. *Journal of Allergy and Clinical Immunology* 124 (6), 1129–1138.
- Hospach, T., Lohse, P., Heilbronner, H., Dannecker, G.E., Lohse, P., 2005. Pseudodominant inheritance of the hyperimmunoglobulinemia D with periodic fever syndrome in a mother and her two monozygotic twins. *Arthritis and Rheumatism* 52 (11), 3606–3610.
- Houten, S.M., Wanders, R.J., Waterham, H.R., 2000. Biochemical and genetic aspects of mevalonate kinase and its deficiency. *Biochimica et Biophysica Acta* 1529 (1–3), 19–32.
- Klasen, I.S., Göertz, J.H., van de Wiel, G.A., Weemaes, C.M., van der Meer, J.W., Drenth, J.P., 2001. Hyper-immunoglobulin A in the hyperimmunoglobulinemia D syndrome. *Clinical and Diagnostic Laboratory Immunology* 8 (1), 58–61.
- Korppi, M., van Gijn, M.E., Anttila, K., 2011. Hyperimmunoglobulinemia D and periodic fever syndrome in children. Review on therapy with biological drugs and case report. *Acta Paediatrica* 100 (1), 21–25.
- Lachmann, H.J., Quartier, P., So, A., Hawkins, P.N., 2011. The emerging role of interleukin-1 β in autoinflammatory diseases. *Arthritis and Rheumatism* 63 (2), 314–324.
- Lierl, M., 2007. Periodic fever syndromes: a diagnostic challenge for the allergist. *Allergy* 62 (12), 1349–1358.
- Rigante, D., Ansuini, V., Bertoni, B., Pugliese, A.L., Avallone, L., Federico, G., Stabile, A., 2006. Treatment with anakinra in the hyperimmunoglobulinemia D/periodic fever syndrome. *Rheumatology International* 27 (1), 97–100.
- Saulsbury, F.T., 2003. Hyperimmunoglobulinemia D, and periodic fever syndrome (HIDS) in a child with normal serum IgD, but increased serum IgA concentration. *Journal of Pediatrics* 143 (1), 127–129.
- Stojanov, S., Kastner, D.L., 2005. Familial autoinflammatory diseases: genetics, pathogenesis and treatment. *Current Opinion in Rheumatology* 17 (5), 586–599.
- Touitou, I., Koné-Paut, I., 2008. Autoinflammatory diseases. *Best Practice & Research. Clinical Rheumatology* 22 (5), 811–829.
- van der Burgh, R., Ter Haar, N.M., Boes, M.L., Frenkel, J., 2012. Mevalonate kinase deficiency, a metabolic autoinflammatory disease. *Clinical Immunology* S1521–6616 (12), 00236–00237.
- van der Hilst, J.C., Frenkel, J., 2010. Hyperimmunoglobulin D syndrome in childhood. *Current Rheumatology Reports* 12 (2), 101–107.